Prediction of Protein-Protein Complexes by Computational Docking and Amide Hydrogen/Deuterium Exchange

Law, Dennis S., Anand, Ganesh S., Mandell, Jeffrey G., Snead, Aaron N., Tsigelny, Igor, Taylor, Susan S., Ten Eyck, Lynn F.*, Komives, Elizabeth A.

Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, CA, USA

An important goal of structural biology is to build-up the structures of higher-order protein-protein complexes from structures of the individual subunits. Often structures or higher order complexes are difficult to obtain by crystallography. We have used an alternative approach in which the structures of the individual catalytic (C) subunit and regulatory subunit ($R^{I}\alpha$(94-244)) of protein kinase A (PKA) were first subjected to computational docking, and the top 100,000 solutions were subsequently filtered based on amide hydrogen/deuterium ($H/^{2}H$) exchange interface protection data. The resulting set of filtered solutions forms an ensemble of structures in which, besides the inhibitor peptide binding site, a flat interface between the C-terminal lobe of the C-subunit and the A- and B-helices of RI£\(94-244) is uniquely identified. This holoenzyme structure satisfies all previous experimental data on the complex, and allows prediction of new contacts between the two subunits.

The procedure has many advantages over more conventional methods. It is much faster than *de novo* determination of the structures of the complex by crystallography of NMR. The $H/^{2}H$ exchange procedure provides a good estimate of conformational changes, which if undetected can lead to incorrect interpretations of the computational docking procedures. Most importantly, the method gives results that are subject to experimental testing by standard techniques such as mutagenesis.